# Clinical Application of Biomarkers in Obstructive HCM: Insights from SEQUOIA-HCM


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# Background: Aficamten is a Next-in-Class Cardiac Myosin Inhibitor

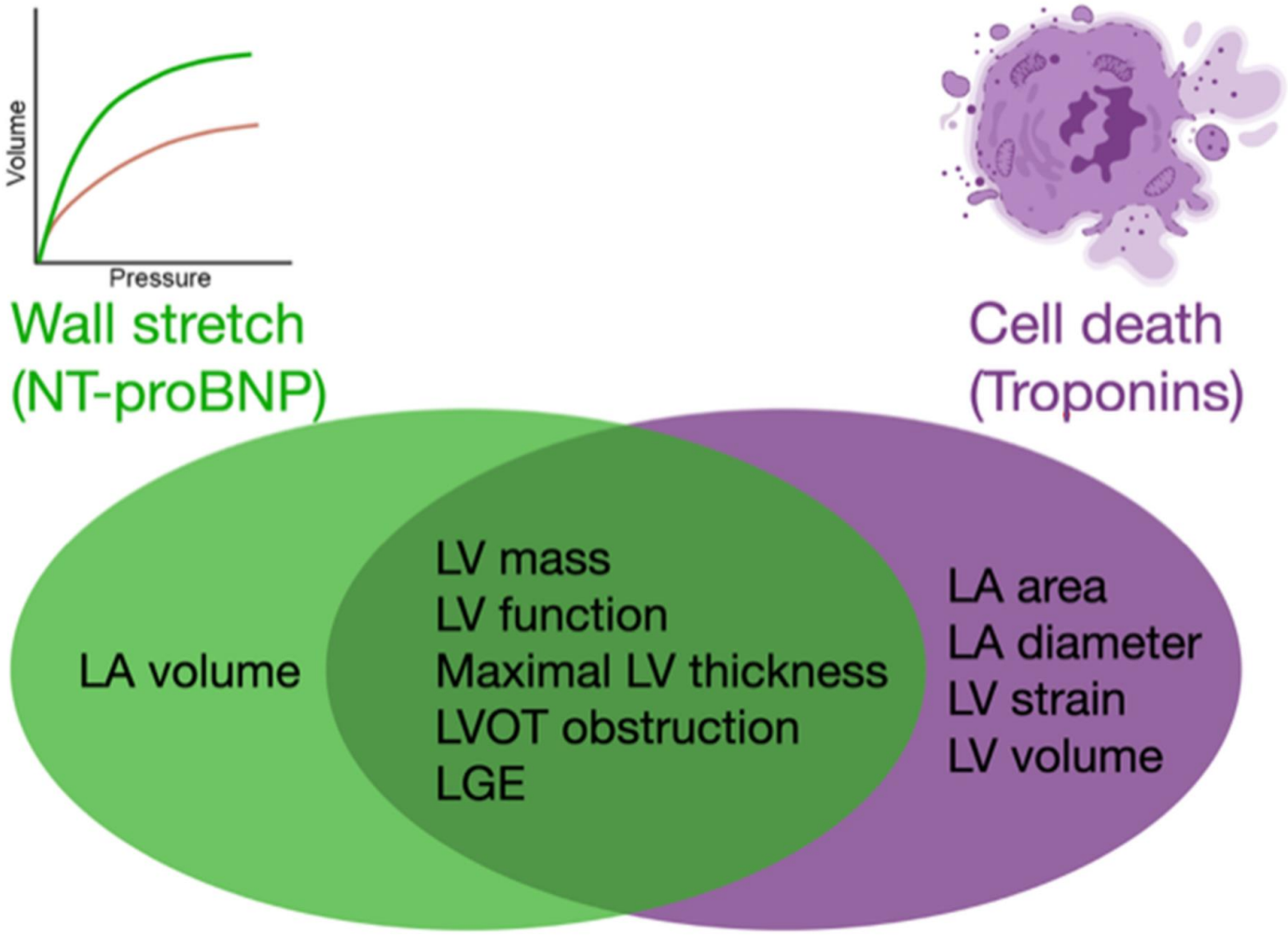

- Aficamten is an investigational, novel, cardiac myosin inhibitor targeting the **hypercontractility** seen in patients with obstructive hypertrophic cardiomyopathy (oHCM).
- Aficamten was engineered with the goal of achieving specific pharmacologic properties that allow for flexible dosing and optimal safety.
  - **A half-life of ~3.4 days** → steady state by 2 weeks, rapid dose titration, and reversibility.
  - **A predictable and shallow dose–response relationship**.
  - **Low liability for drug-drug interactions** due to metabolism via multiple cytochrome P450 enzymes.



Chuang C, et al. J Med Chem 2021:64(19):14142-52.

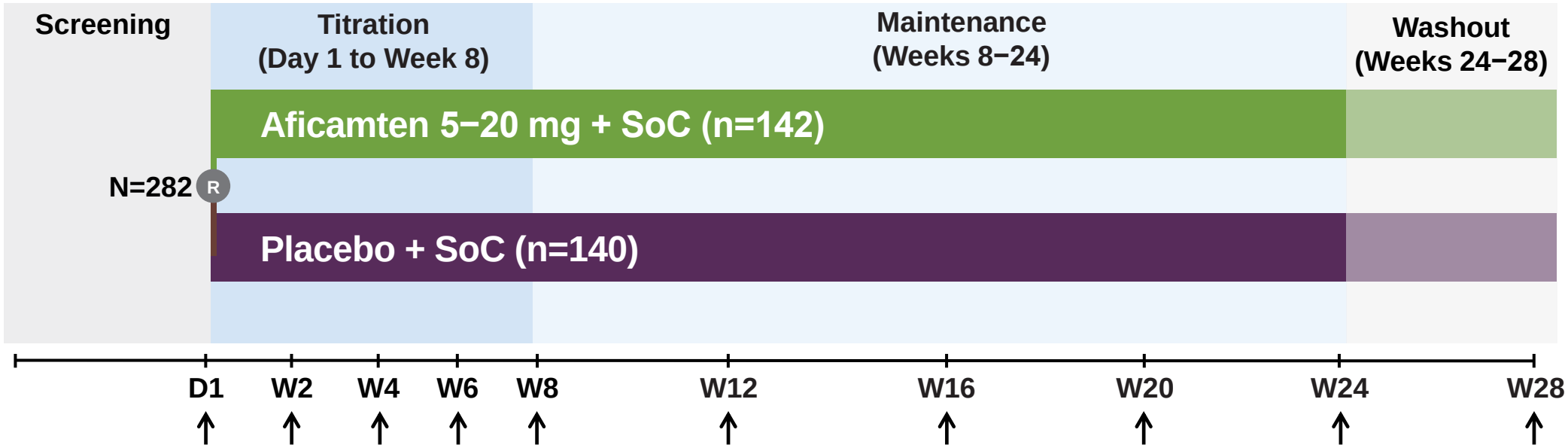
# Background: Biomarkers in Hypertrophic Cardiomyopathy

- Multiple studies have shown circulating cardiac biomarkers are associated with key pathophysiologic processes in HCM.
- Troponins and natriuretic peptides correlate with adverse prognosis and heart failure symptoms in HCM.
- It is unknown if biomarker testing provides insights into treatment for oHCM.




LA, left atrium; LGE, late gadolinium enhancement; LV, left ventricle; LVOT, left ventricular outflow tract; HCM, hypertrophic cardiomyopathy; NT-proBNP, N-terminal pro-B type natriuretic peptide.

# Methods: SEQUOIA-HCM Study Design and Objectives




- Aficamten dose was adjusted to achieve Valsalva LVOT-G <30 mmHg while maintaining LVEF ≥50%.
- Clinical assessments, including cardiac biomarkers, were measured at baseline, each dose titration (Weeks 2, 4, and 6), every 4 weeks during treatment, and after 4 weeks drug washout.
- SEQUOIA-HCM met its primary endpoint: improved $pVO_2$ at Week 24, measured by cardiopulmonary exercise testing.

Black arrows indicate timing of clinical and biomarker assessments.
LVEF, left ventricular ejection fraction; LVOT-G, LVOT gradient; $pVO_2$, peak oxygen uptake; R, randomized (1:1) in a blinded manner; SoC, standard of care.
Maron MS, et al. *N Engl J Med* 2024;390(20):1849-61.

# Methods: SEQUOIA-HCM Study Design and Objectives

- This pre-specified secondary analysis of SEQUOIA-HCM describes the impact of aficamten on cardiac biomarkers.

- Our specific objectives were to:
  1. Describe associations between baseline NT-proBNP and hs-cTnI concentrations and patient characteristics.
  2. Assess the relationship between changes in cardiac biomarkers and efficacy endpoints during aficamten treatment and after drug washout.
  3. Test the hypothesis that the 2 week change in cardiac biomarkers is associated with response to treatment.

# Results: Baseline Characteristics

| | Overall |
|---|---|
| | n=282 |
| **Age, y** | 59.1 ± 12.9 |
| **Female sex** | 115 (40.8) |
| **BMI, kg/m$^2$** | 28.1 ± 3.7 |
| **Race, White** | 223 (79.1) |
| **Biomarker concentrations, median [IQR]** | |
| **NT-proBNP, ng/L** | 788 [346, 1699] |
| **hs-cTnI, ng/L** | 12 [8, 27] |
| **Background HCM therapy** | |
| **Beta-blockers** | 173 (61.3) |
| **Calcium-channel blockers** | 81 (28.7) |
| **Disopyramide** | 36 (12.8) |
| **ICD** | 39 (13.8) |
| **Background health status** | |
| **pVO$_2$, mL/kg/min** | 18.5 ± 4.5 |
| **KCCQ-CSS** | 74.7 ± 18.0 |
| **NYHA FC II** | 214 (75.9) |
| **Echocardiogram** | |
| **Resting LVOT-G, mmHg** | 55.1 ± 29.6 |
| **Valsalva LVOT-G, mmHg** | 83.1 ± 32.3 |
| **LVEF, %** | 74.8 ± 5.9 |
| **Maximal LV wall thickness, cm** | 2.09 ± 0.30 |

Data shown as mean ± SD or n (%) unless otherwise specified.

BMI, body mass index; ICD, implantable cardioverter defibrillator; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; NYHA FC, New York Heart Association functional class.

# Results: Baseline Characteristics

| | Overall | NT-proBNP | |
|---|---|---|---|
| | n=282 | Below Median, n=139 | Above Median, n=138 |
| **Age, y** | 59.1 ± 12.9 | 57.6 ± 12.0 | 60.4 ± 13.8 |
| **Female sex** | 115 (40.8) | 40 (28.8) | 72 (52.2) |
| **BMI, kg/m$^2$** | 28.1 ± 3.7 | 29.0 ± 3.3 | 27.1 ± 3.9 |
| **Race, White** | 223 (79.1) | 109 (78.4) | 109 (79.0) |
| **Biomarker concentrations, median [IQR]** | | | |
| **NT-proBNP, ng/L** | 788 [346, 1699] | 346 [219, 521] | 1714 [1087, 2709] |
| **hs-cTnI, ng/L** | 12 [8, 27] | 10 [6,19] | 16 [10, 38] |
| **Background HCM therapy** | | | |
| **Beta-blockers** | 173 (61.3) | 75 (54.0) | 95 (68.8) |
| **Calcium-channel blockers** | 81 (28.7) | 43 (30.9) | 37 (26.8) |
| **Disopyramide** | 36 (12.8) | 13 (9.4) | 23 (16.7) |
| **ICD** | 39 (13.8) | 16 (11.5) | 22 (15.9) |
| **Background health status** | | | |
| **pVO$_2$, mL/kg/min** | 18.5 ± 4.5 | 19.5 ± 4.4 | 17.5 ± 4.4 |
| **KCCQ-CSS** | 74.7 ± 18.0 | 75 ± 17 | 75 ± 20 |
| **NYHA FC II** | 214 (75.9) | 107 (77.0) | 102 (73.9) |
| **Echocardiogram** | | | |
| **Resting LVOT-G, mmHg** | 55.1 ± 29.6 | 46 ± 26 | 64 ± 30 |
| **Valsalva LVOT-G, mmHg** | 83.1 ± 32.3 | 76 ± 31 | 90 ± 32 |
| **LVEF, %** | 74.8 ± 5.9 | 75 ± 6 | 74 ± 6 |
| **Maximal LV wall thickness, cm** | 2.09 ± 0.30 | 2.04 ± 0.27 | 2.14 ± 0.33 |

Data shown as mean ± SD or n (%) unless otherwise specified.

BMI, body mass index; ICD, implantable cardioverter defibrillator; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; NYHA FC, New York Heart Association functional class.

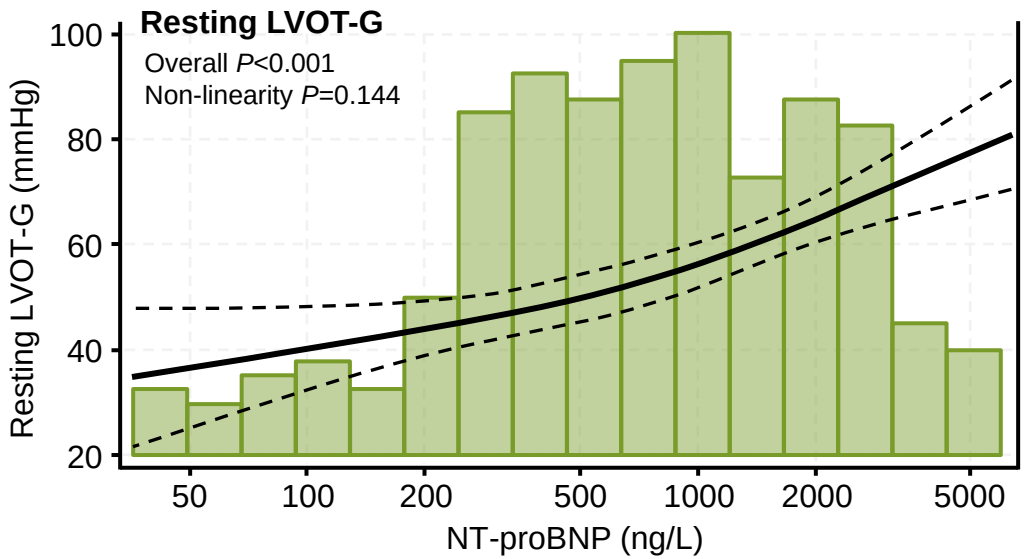
# Results: Baseline Characteristics

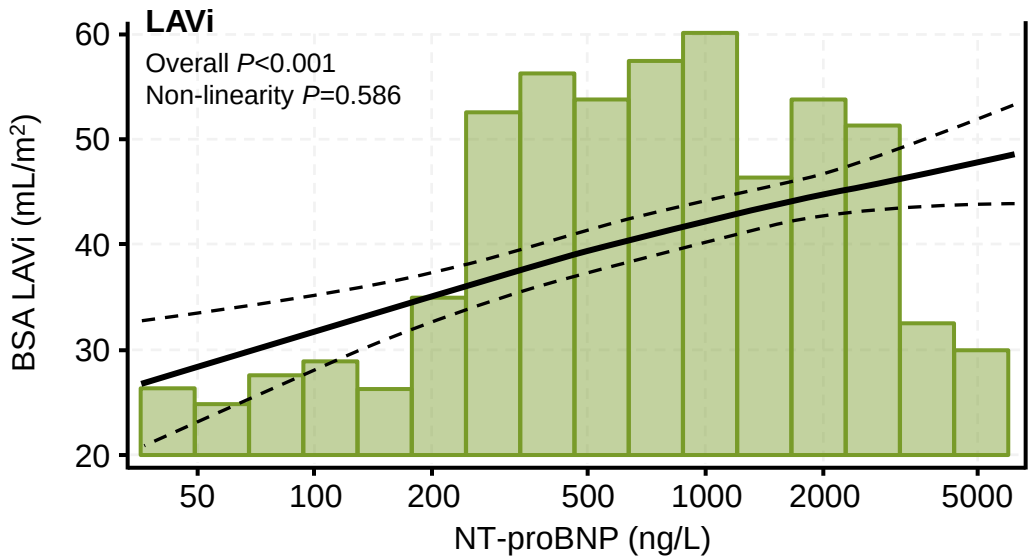
| | Overall | NT-proBNP | | hs-cTnI | |
|---|---|---|---|---|---|
| | n=282 | Below Median, n=139 | Above Median, n=138 | Below Median, n=136 | Above Median, n=134 |
| **Age, y** | 59.1 ± 12.9 | 57.6 ± 12.0 | 60.4 ± 13.8 | 60.3 ± 12.2 | 57.6 ± 13.5 |
| **Female sex** | 115 (40.8) | 40 (28.8) | 72 (52.2) | 68 (50.0) | 40 (29.9) |
| **BMI, kg/m$^2$** | 28.1 ± 3.7 | 29.0 ± 3.3 | 27.1 ± 3.9 | 28.5 ± 3.8 | 27.6 ± 3.6 |
| **Race, White** | 223 (79.1) | 109 (78.4) | 109 (79.0) | 115 (84.6) | 98 (73.1) |
| **Biomarker concentrations, median [IQR]** | | | | | |
| **NT-proBNP, ng/L** | 788 [346, 1699] | 346 [219, 521] | 1714 [1087, 2709] | 511 [279, 1112] | 1064 [542, 2359] |
| **hs-cTnI, ng/L** | 12 [8, 27] | 10 [6,19] | 16 [10, 38] | 8 [5, 10] | 28 [17, 68] |
| **Background HCM therapy** | | | | | |
| **Beta-blockers** | 173 (61.3) | 75 (54.0) | 95 (68.8) | 90 (66.2) | 74 (55.2) |
| **Calcium-channel blockers** | 81 (28.7) | 43 (30.9) | 37 (26.8) | 33 (24.3) | 46 (34.3) |
| **Disopyramide** | 36 (12.8) | 13 (9.4) | 23 (16.7) | 21 (15.4) | 13 (9.7) |
| **ICD** | 39 (13.8) | 16 (11.5) | 22 (15.9) | 16 (11.8) | 22 (16.4) |
| **Background health status** | | | | | |
| **pVO$_2$, mL/kg/min** | 18.5 ± 4.5 | 19.5 ± 4.4 | 17.5 ± 4.4 | 18.0 ± 4.3 | 19.0 ± 4.6 |
| **KCCQ-CSS** | 74.7 ± 18.0 | 75 ± 17 | 75 ± 20 | 72 ± 18 | 77 ± 18 |
| **NYHA FC II** | 214 (75.9) | 107 (77.0) | 102 (73.9) | 98 (72.1) | 105 (78.4) |
| **Echocardiogram** | | | | | |
| **Resting LVOT-G, mmHg** | 55.1 ± 29.6 | 46 ± 26 | 64 ± 30 | 54 ± 30 | 56 ± 30 |
| **Valsalva LVOT-G, mmHg** | 83.1 ± 32.3 | 76 ± 31 | 90 ± 32 | 82 ± 33 | 85 ± 32 |
| **LVEF, %** | 74.8 ± 5.9 | 75 ± 6 | 74 ± 6 | 75 ± 5 | 74 ± 6 |
| **Maximal LV wall thickness, cm** | 2.09 ± 0.30 | 2.04 ± 0.27 | 2.14 ± 0.33 | 1.99 ± 0.24 | 2.18 ± 0.33 |

Data shown as mean ± SD or n (%) unless otherwise specified.

BMI, body mass index; ICD, implantable cardioverter defibrillator; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score; NYHA FC, New York Heart Association functional class.

# Results: Clinical Variables That Predict Baseline NT-proBNP Concentration

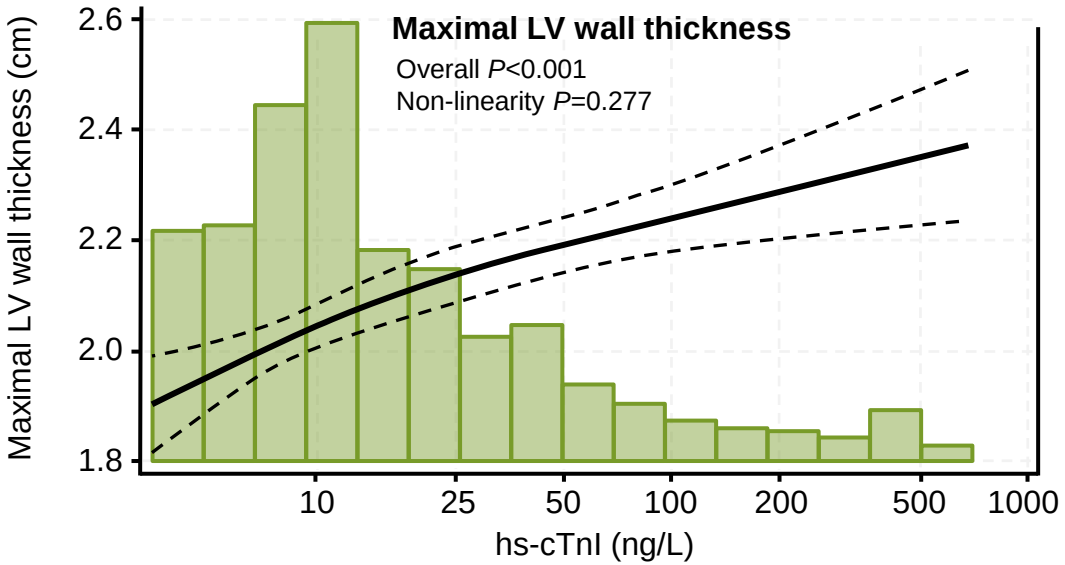


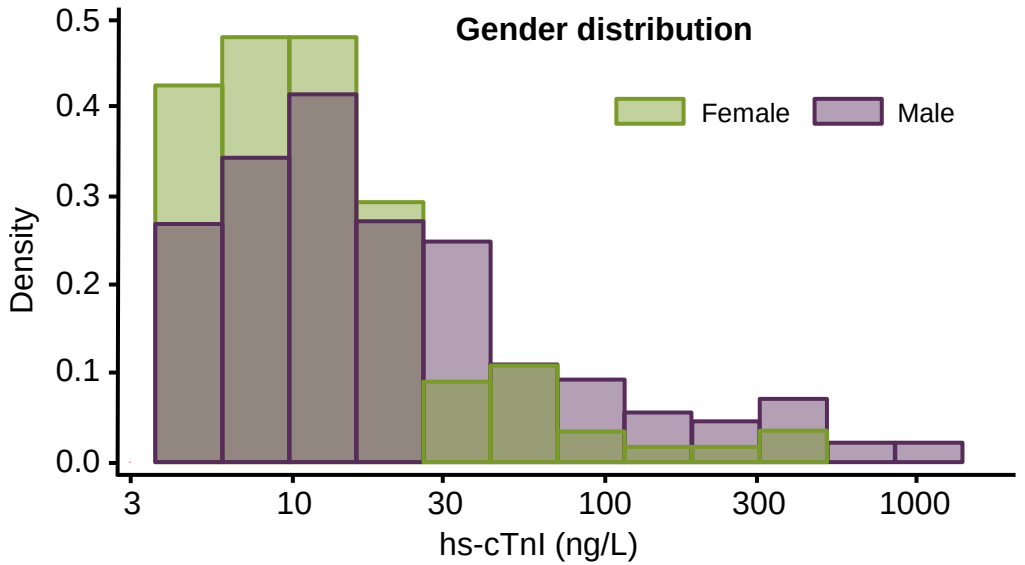




| Predictors of baseline NT-proBNP, n=266 | Association (95% CI) | \|Z\| | *P* value |
|---|---|---|---|
| hs-cTnI (per log) | +35% (+23%, +47%) | 6.7 | <0.001 |
| LAVi (per SD) | +30% (+17%, +45%) | 4.9 | <0.001 |
| E/e´ septal (per SD) | +31% (+17%, +47%) | 4.6 | <0.001 |
| Resting LVOT-G (per SD) | +23% (+10%, +37%) | 3.7 | <0.001 |
| BMI (per 5 kg/m$^2$) | –24% (–34%, –13%) | 3.9 | <0.001 |
| Female sex | +48% (+18%, +86%) | 3.4 | 0.001 |

E/e´, the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; LAVi, left atrial volume index.

# Results: Clinical Variables that Predict Baseline hs-cTnI Concentration

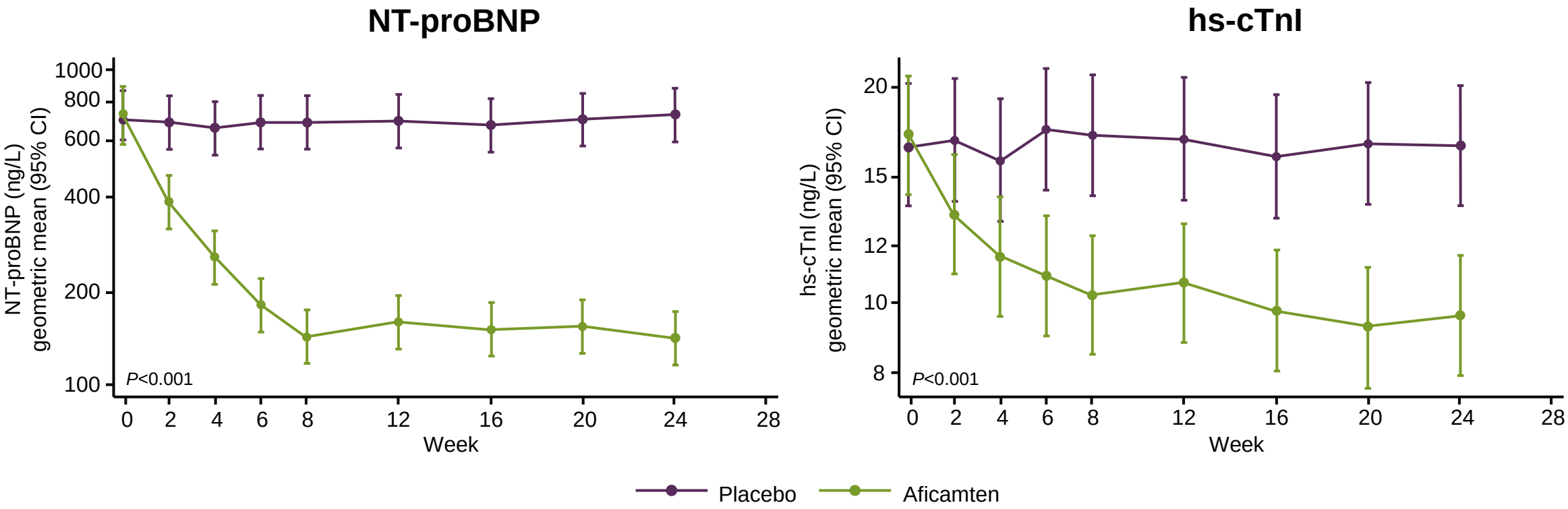



| Predictors of baseline hs-cTnI, n=266 | Association (95% CI) | \|Z\| | *P* value |
|---|---|---|---|
| NT-proBNP (per log) | +41% (+25%, +59%) | 5.6 | <0.001 |
| Female sex | −48% (−61%, −32%) | 4.7 | <0.001 |
| Maximal LV wall thickness (per SD) | +33% (+17%, +52%) | 4.3 | <0.001 |

hs-cTnI assay reference upper limit is 14 ng/L for females and 35 ng/L for males.

# Results: Effect of Aficamten on Biomarkers in SEQUOIA-HCM




Baseline 788 ng/L (IQR, 346–1699)

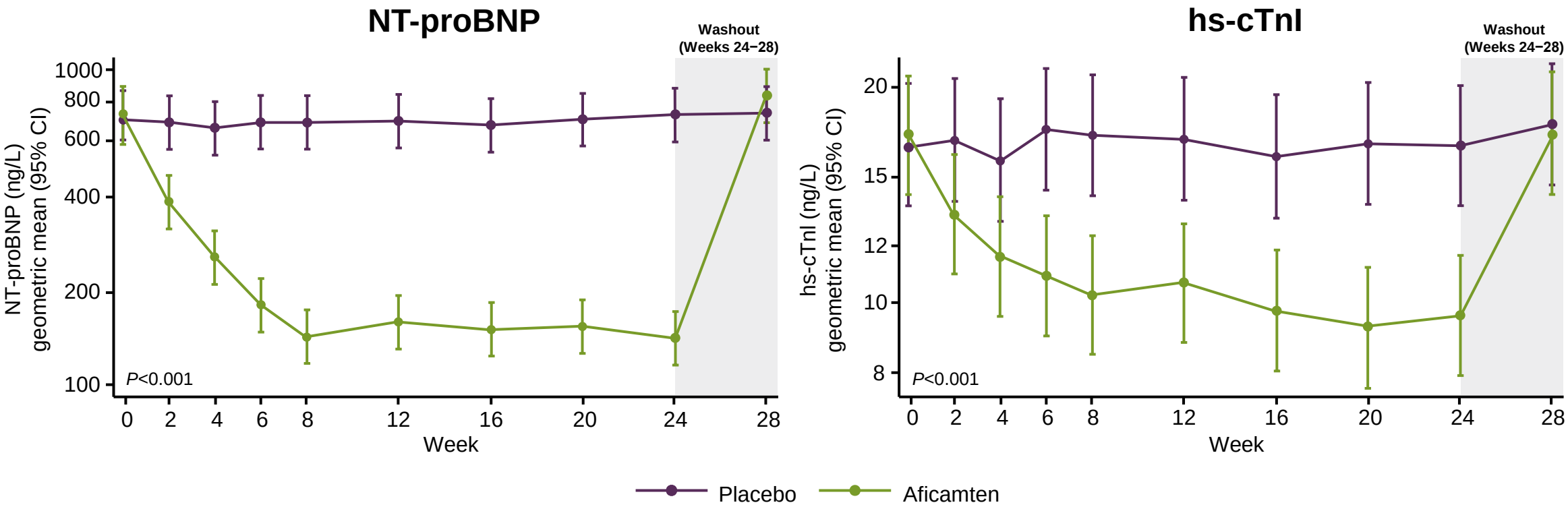
**80% reduction** over 24 weeks

Baseline 12.1 ng/L (IQR, 7.7–27.3)

**43% reduction** over 24 weeks

IQR, interquartile range.

# Results: Effect of Aficamten on Biomarkers in SEQUOIA-HCM




Baseline 788 ng/L (IQR, 346–1699)

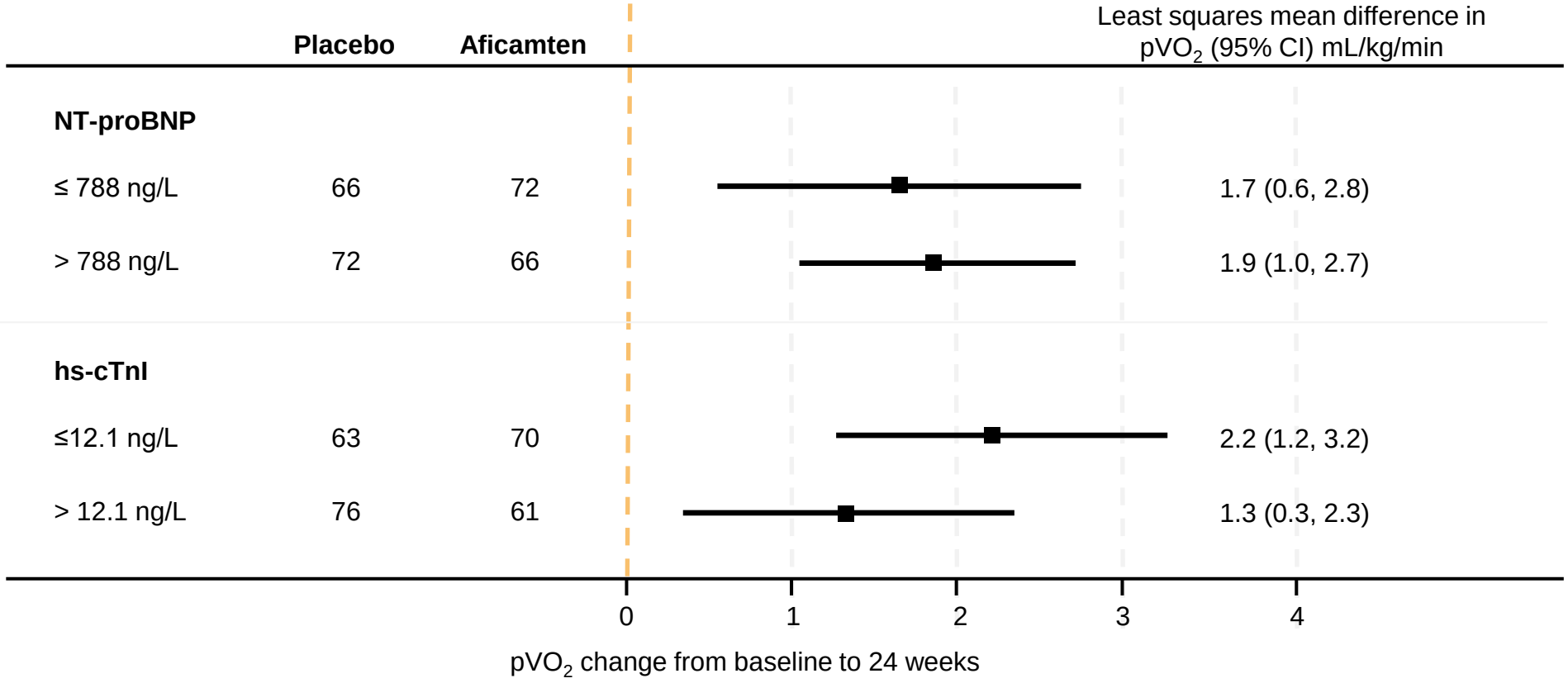
**80% reduction** over 24 weeks

Baseline 12.1 ng/L (IQR, 7.7–27.3)

**43% reduction** over 24 weeks

IQR, interquartile range.

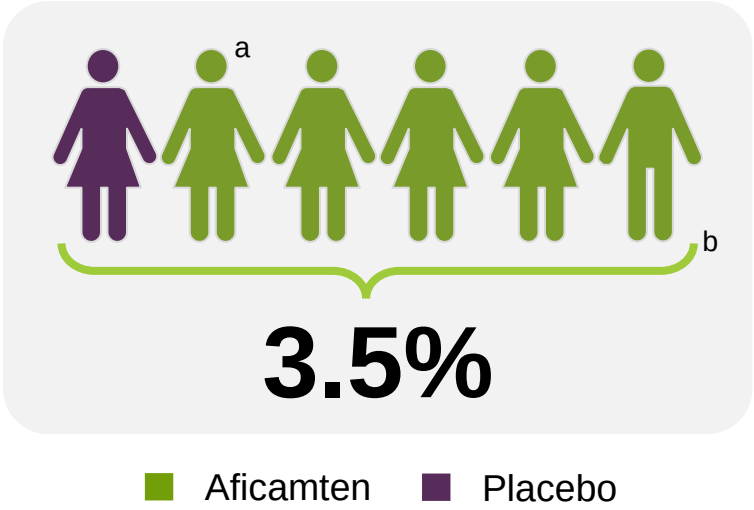
# Results: Improvement in Exercise Capacity Is Consistent Irrespective of Baseline Baseline Biomarkers




**Aficamten improved $pVO_2$ irrespective of baseline biomarkers**

# Results: Baseline NT-proBNP and hs-cTnI did not Predict Future LVEF <50%

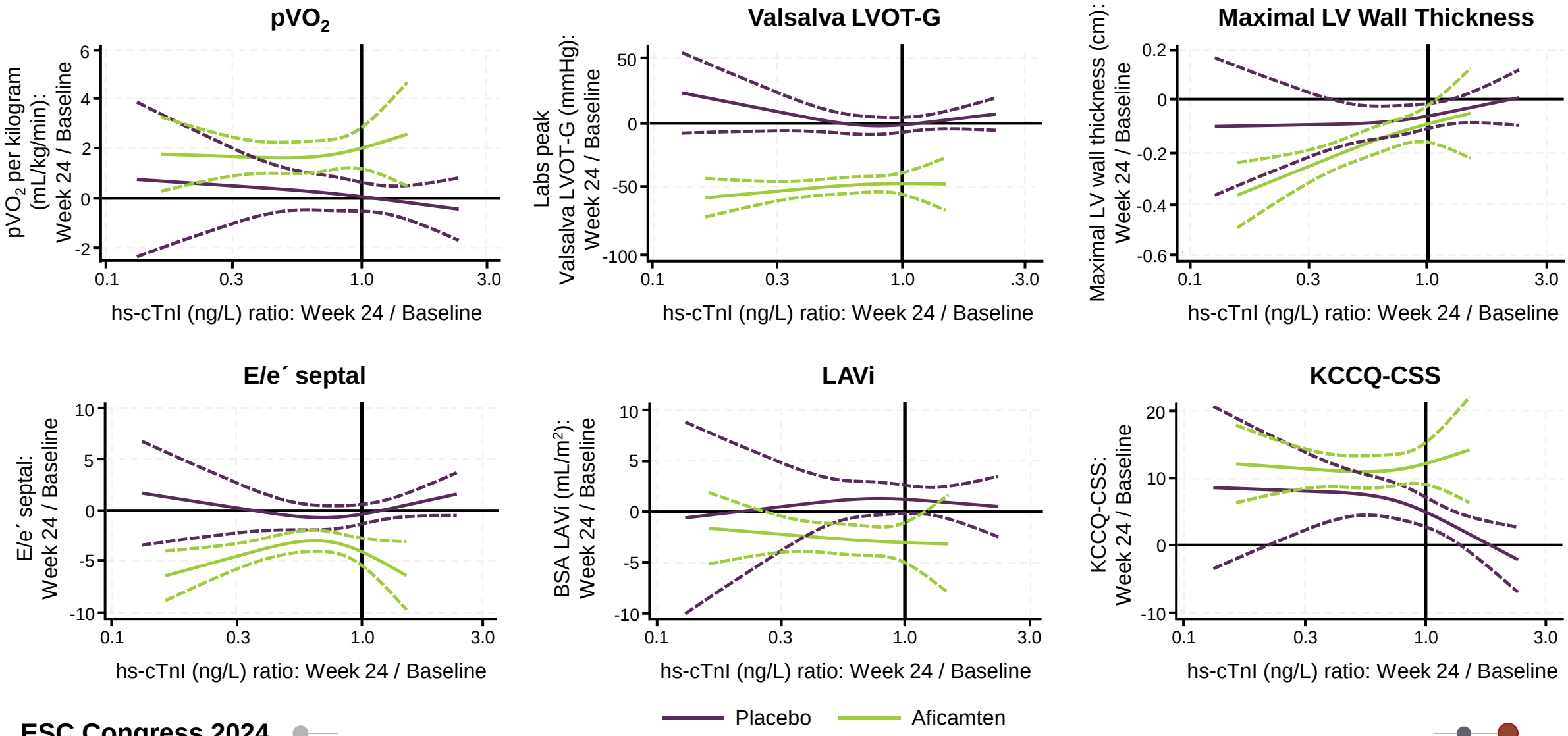
**Core Laboratory LVEF <50%**
**(1º Analysis)**




- LVEF <50% was an event of special interest in SEQUOIA-HCM.
- No aficamten-treated patient with LVEF <50% experienced heart failure.
- Only 1 patient with LVEF <50% had an increase in NT-proBNP (also had COVID-19).
  - NT-proBNP 43 ng/L (baseline) → 154 ng/L

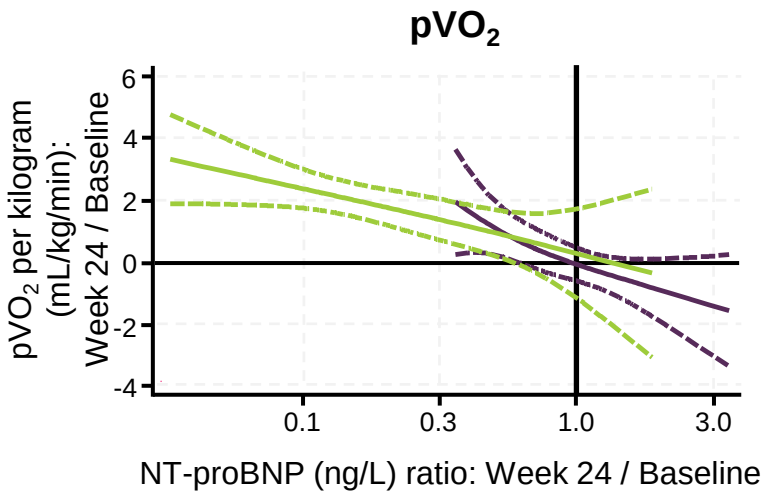
[a] COVID-19 infection preceded LVEF <50% based on both core and site laboratory assessments.
[b] Did not undergo dose adjustment.

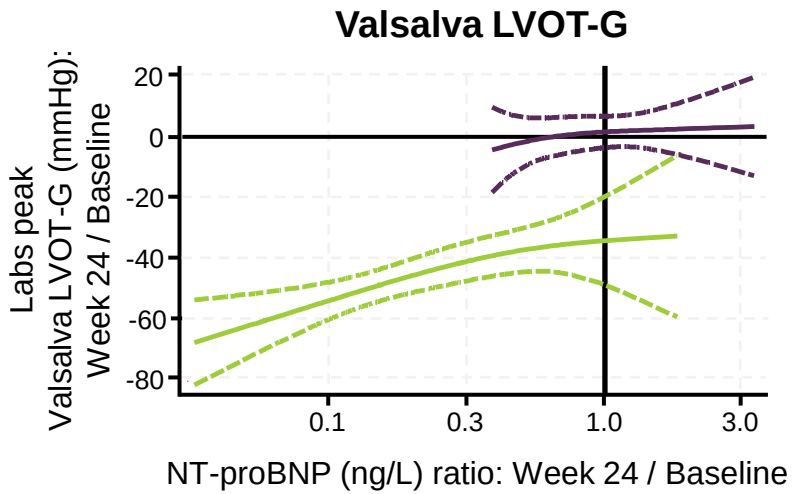
# Results: Relationship Between Changes in hs-cTnI Concentration and Other Clinical Measures (Ratio of Week 24 to Baseline)

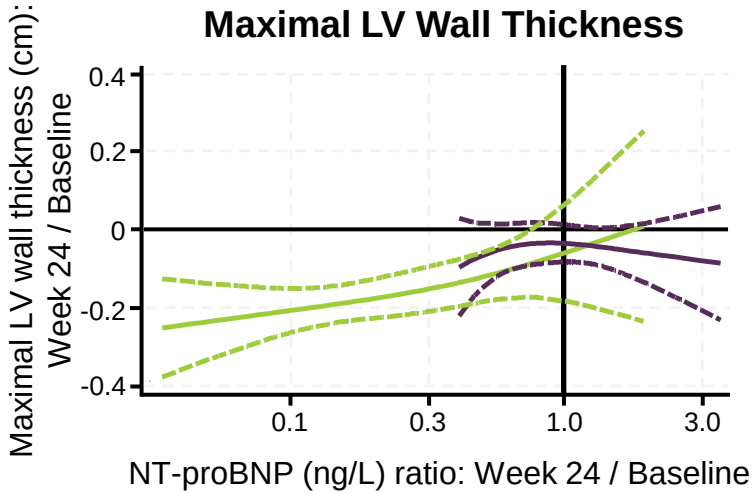


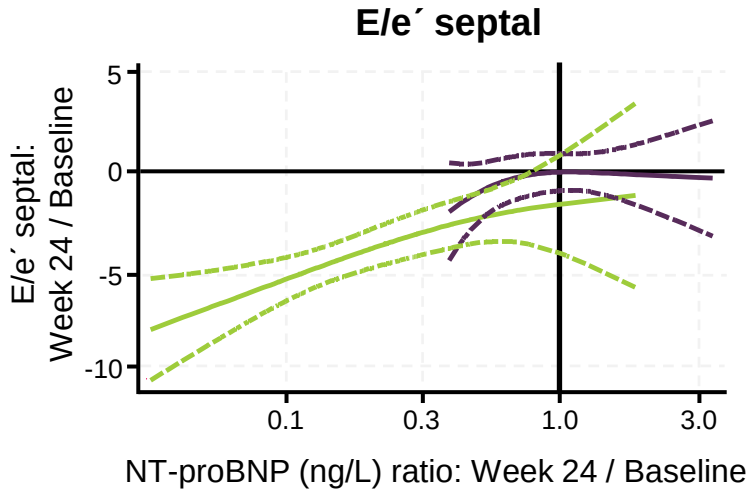

Solid and dotted lines show the association correlate with 95% CIs. Black vertical lines at 1 and horizontal lines at 0 indicate no change from baseline.

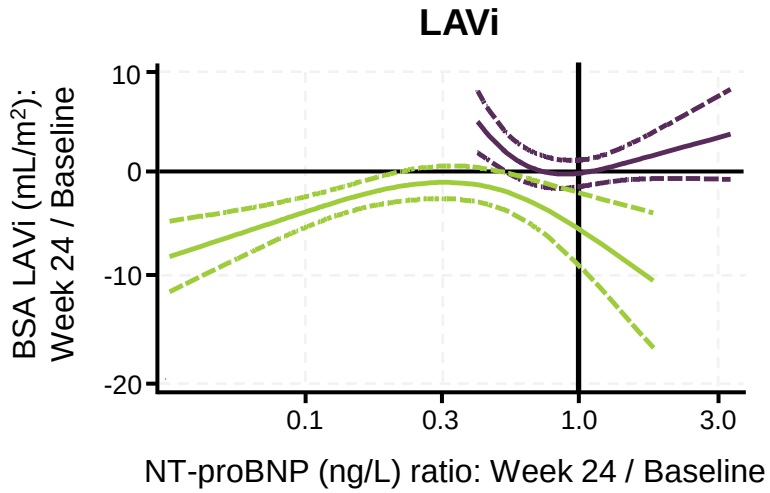
# Results: Relationship Between Changes in NT-proBNP Concentration and Other Clinical Measures (Ratio of Week 24 to Baseline)

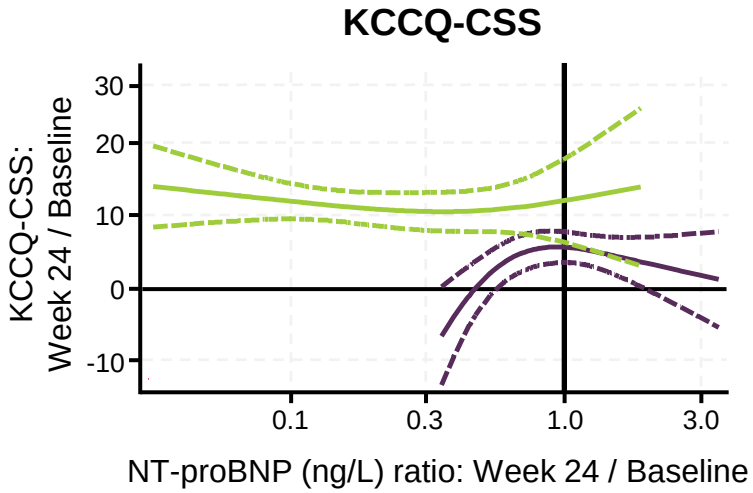


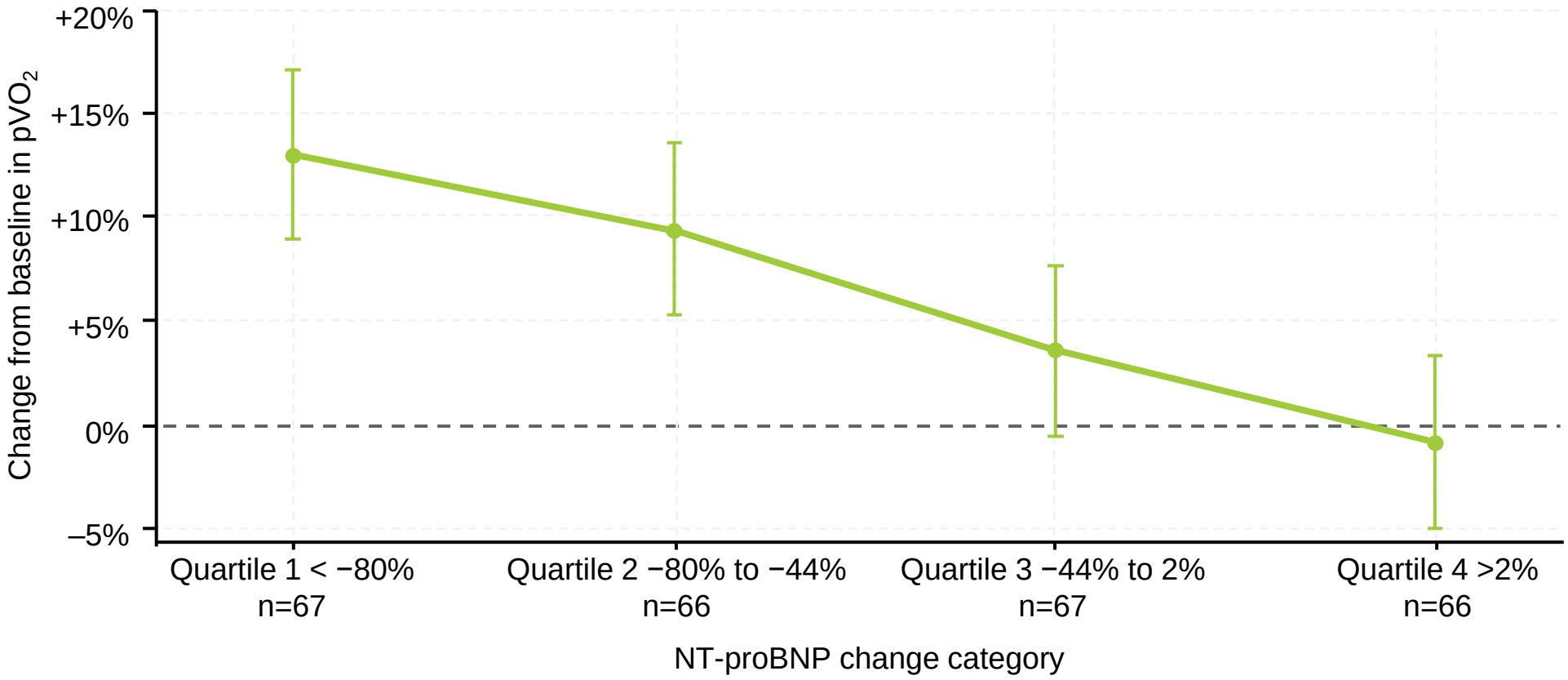




Placebo Aficamten

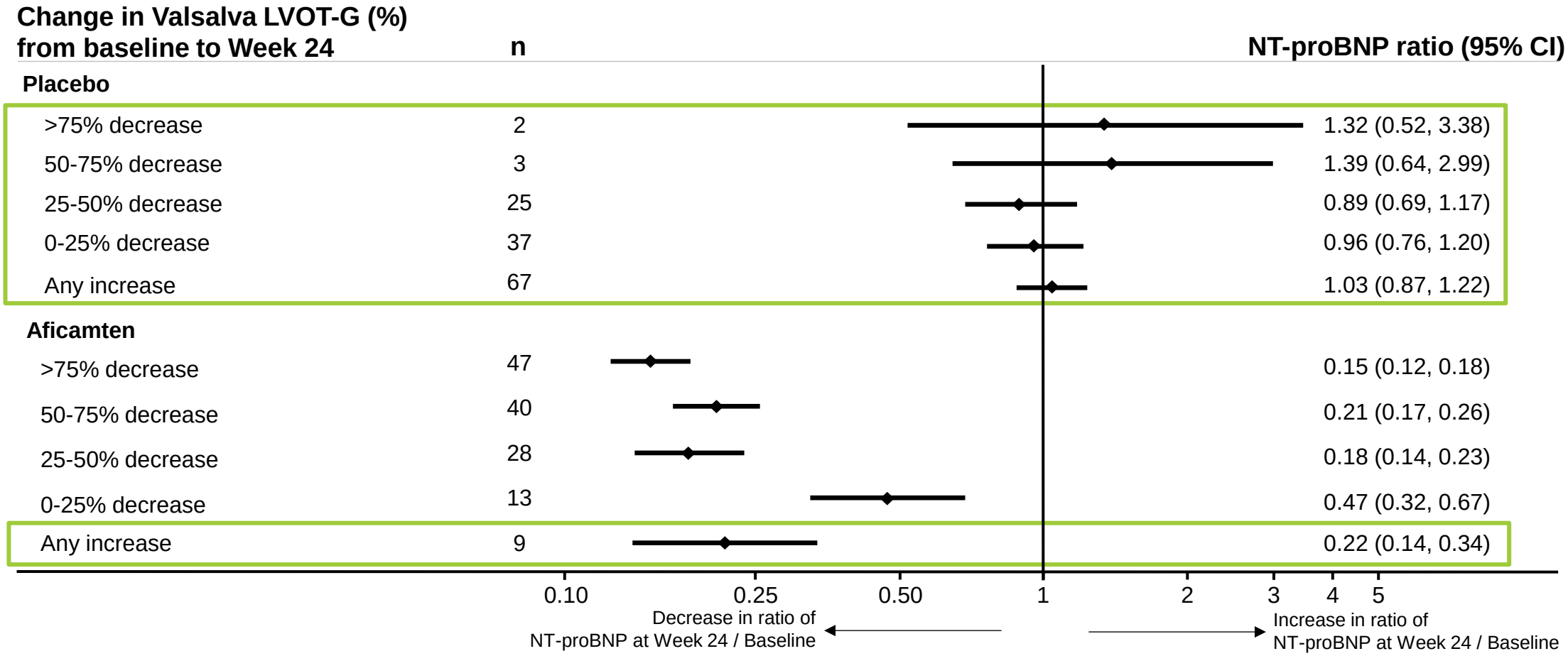
Solid and dotted lines show the association correlate with 95% CIs. Black vertical lines at 1 and horizontal lines at 0 indicate no change from baseline.

# Results: An Inverse Linear Association Between Relative Change in NT-proBNP and Change in $pVO_2$




**Change in NT-proBNP by 24 weeks was an accurate surrogate for change in $pVO_2$**

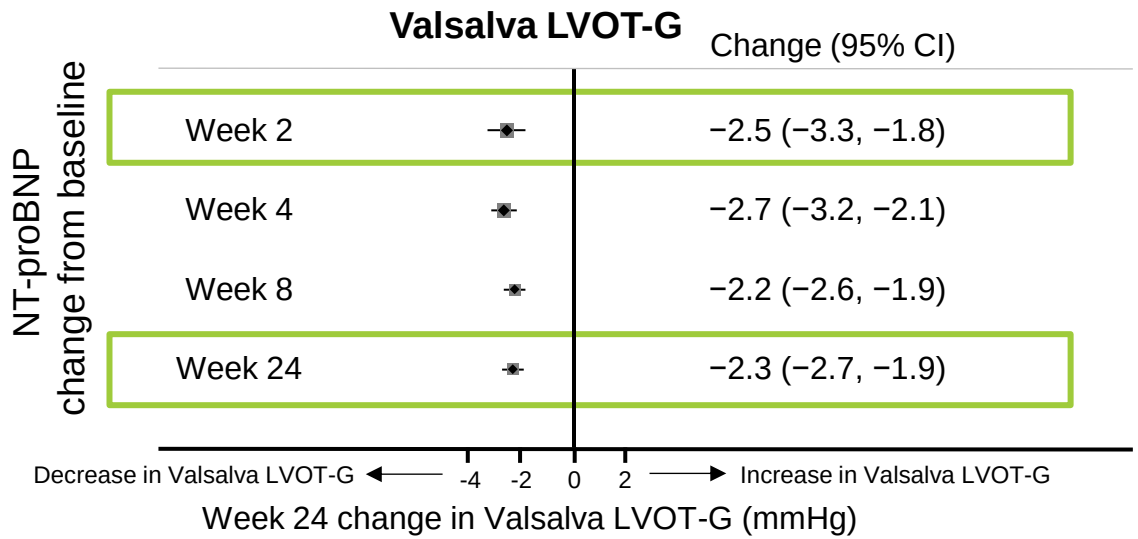
# Results: An Inverse Linear Association Between Relative Change in NT-proBNP and Change in LVOT-G

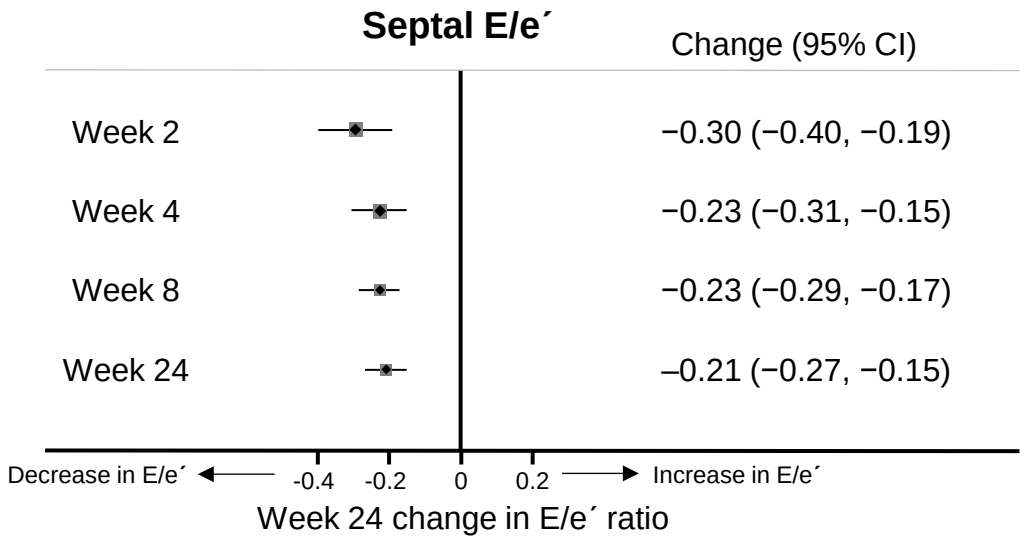


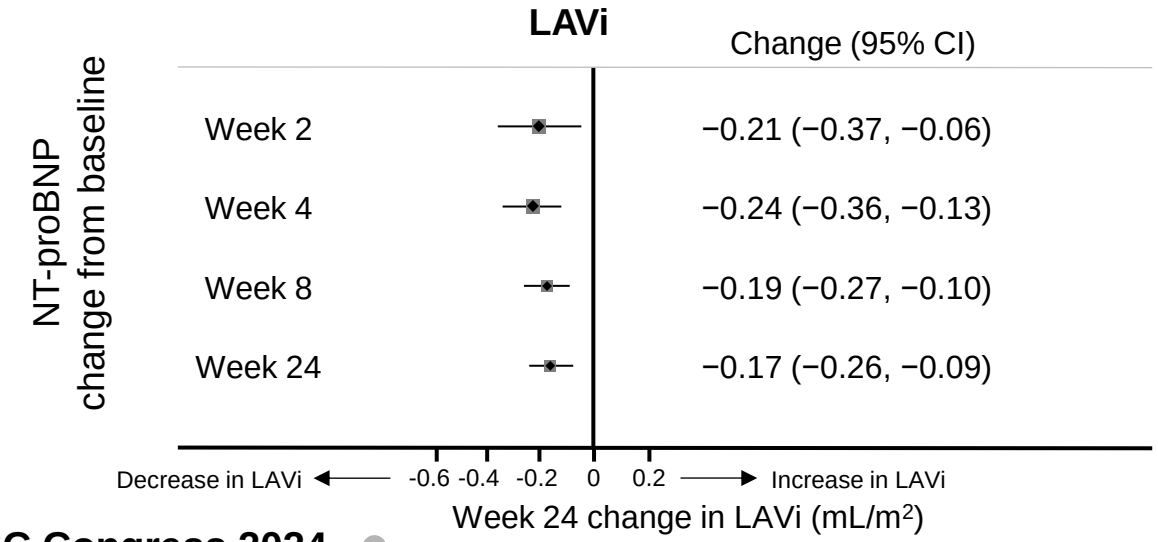

**The NT-proBNP decrease may not be directly caused by lower LVOT-G**

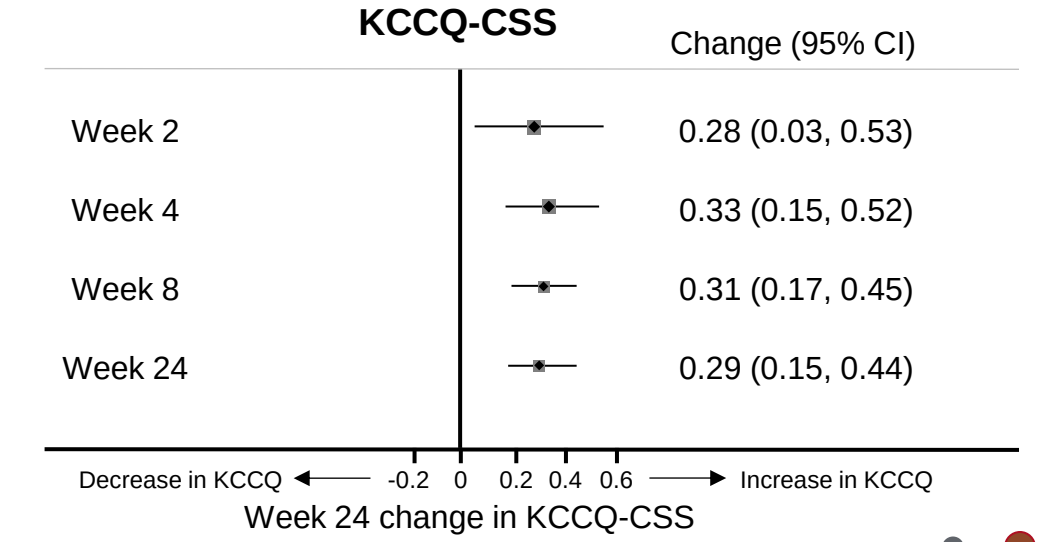
Solid black vertical line indicates no treatment effect

# Results: Week 2 Change in NT-proBNP Was Associated With Week 24 Change in Clinical Outcomes




Solid black vertical line indicates no treatment effect. Results are expressed per 10% reduction in NT-proBNP.

# Conclusions

- In SEQUOIA-HCM, concentrations of NT-proBNP and hs-cTnI were associated with relevant clinical and echocardiographic measurements at baseline.
- After 24 weeks of treatment, aficamten resulted in an 80% reduction in NT-proBNP and 43% reduction in hs-cTnI with concentrations returning to baseline after washout.
- Reductions in NT-proBNP and hs-cTnI with aficamten treatment were strongly associated with lowering of LVOT-G, improvement in health status and increased $pVO_2$.
- The change in NT-proBNP concentration by Week 2 was associated with 24-week change in key clinical outcomes.

Clinicians may consider the use of NT-proBNP to monitor functional and qualitative response to aficamten

# Acknowledgments

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We thank the following individuals for their contributions to this clinical trial:

- Participants and their families
- Investigators and study site staff
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# Simultaneous Publication in *EHJ*

**Cardiac biomarkers and effects of aficamten in obstructive hypertrophic cardiomyopathy: the SEQUOIA-HCM trial**

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